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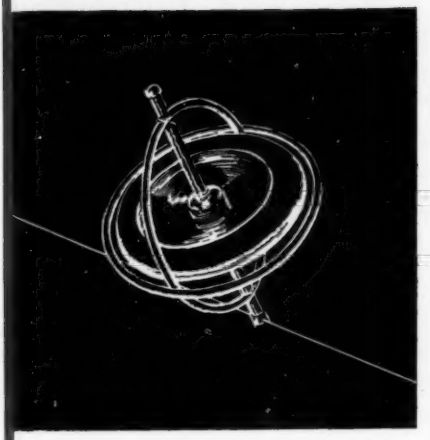

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CONTENTS

E D I T O R I A L

ADEQUATE DIRECTIONS FOR USE

THE famous Sullivan case has established the prerogative of the Food and Drug Administration to control the sale and the labeling of a drug until it reaches the ultimate consumer, providing that at some time it has passed in interstate commerce.

There are those who feel that such power abrogates states' rights but since this decision has withstood the final test of the Supreme Court it is not likely that any change will be made in the future. The Court based its decision, apparently, on it being more important to protect the consumer than states' rights. Whether or not this reasoning is correct is a matter of opinion but the ruling of the Court stands, nevertheless, unless the Food, Drug and Cosmetic Act is repealed and this is not likely.

The full impact of this decision on the retail pharmacist has not been appreciated. The Sullivan case originated from the sale of a few sulfonamide tablets without adequate directions for use including necessary warning statements. Few pharmacists would condone the sale of such drugs over the counter in the first place and, therefore, they are not concerned with the need for adequate directions for use. As a prescription item sulfonamides need only to be dispensed with the directions for use given on the prescription by the physician. The situation, however, is not so simple. What about the hundreds of items sold every day over the counter to the consumer which carry only a label bearing the name of the drug and the name of the store selling it? Unlike accepted home remedies which have adequate directions for use, many of these drugs are bought by the pharmacist marked "for prescription use only," "for manufacturing purposes only" or "for experimental use only." In these cases what constitutes adequate directions for use? If the importer, wholesaler or manufacturer is loathe to give such information, in what way is the retail pharmacist better qualified? Were

many of these drugs new remedies the circumstances would be understandable but many are drugs used for centuries and sold over the counter for decades bearing the drug name only. In these instances the retail pharmacist is in a quandary for in most cases it is difficult if not impossible for him to ascertain what constitutes adequate directions for use. Should he refuse to continue to sell these drugs even to old established customers who have bought them for years? Should he sell them with a label bearing the drug name only or should be attempt to place on the label adequate directions for use?

If he refuses to sell them he offends his customer. The public accepts the fact that most new drugs cannot be sold over the counter but that a drug they have used for years has suddenly become dangerous they refuse to believe. If the drug is sold with a label bearing the name only it violates the Food, Drug and Cosmetic Act unless it was produced, packaged and distributed in one state and this is rarely so.

If the pharmacist attempts to place on the label adequate directions for use he is confronted with a most difficult task in obtaining such data and then, even after it is assembled, it cannot be put on the ordinary sized label. Finally, the time involved is so extensive that he cannot possibly charge enough to make the sale even cover his costs.

It would appear that this problem is deserving of attention by the A. Ph. A. and the N. A. R. D. and that from these groups should come a coordinated suggestion which will help the retail pharmacist in meeting this problem.

Possibly the time is ripe to discourage all self-medication with drugs so bought by the consumer but we doubt whether public opinion is yet conditioned to such an idealistic plan. The privilege to medicate oneself is still believed by many to be an inalienable right and it would be difficult to change this opinion on any basis. It would be still more difficult to accomplish this with the argument that government regulations make the sale of these drugs over the counter impractical. Such an argument if propounded often enough by the pharmacist might stir up enough public sentiment against the present Food, Drug and Cosmetic Act to do it damage in Congress. This is surely not to be desired but neither is it outside the realm of possibility.

Would it not be ideal if a simple compilation might be prepared listing all drugs that might conceivably be sold over the counter giving in simple, brief and concise language what data should be placed on the label? With this the pharmacist could then comply with the law and do so without great difficulty. If some such plan is not adopted great confusion and contention is certain to result.

L. F. TICE

THE PRODUCTION OF ATEBRIN IN GERMANY

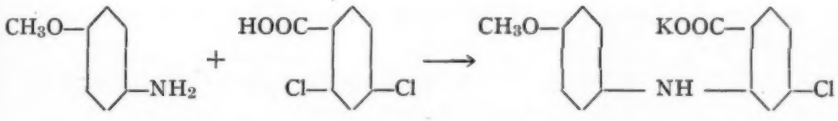
By L. Wilson Greene *

ATEBRIN (atabrine or quinacrine hydrochloride), the synthetic antimalarial which was used widely during the war as a substitute for quinine, was manufactured in Germany at the Elberfeld Plant of the I. G. Farbenindustrie A.-G. This plant had a rated capacity of 1900 kilograms (4180 lbs.) per month in June 1941. Even after the Germans had been driven out of North Africa, the German Government requirement for atebrin amounted to 12,000 kg. (over 26,000 lbs.) per month (1).

The atebrin plant at Elberfeld was visited by an American technical intelligence team, and the information given below was taken from the report of these investigators (2).

The synthesis of this drug was conducted in eight steps, as follows:

1. Preparation of Potassium 4-Chloro-N-(*p*-Methoxyphenyl)-Anthranilate ("Potassium Dicarbon")



The reactor has a capacity of 500 liters and is equipped with a stirrer, a steam jacket, and a reflux condenser.

Into this vessel 30 liters of water and 41 kg. of *p*-anisidine are added. This mixture is warmed to 60-70°C. and is stirred for 15 min., following which 27 kg. of 2,4-dichlorobenzoic acid are introduced. Stirring is continued for 10 min. and 0.36 kg. of copper

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powder is added. Following the copper addition a further portion of the acid (27 kg.) is introduced and the contents of the reactor are stirred for 15 min. more.

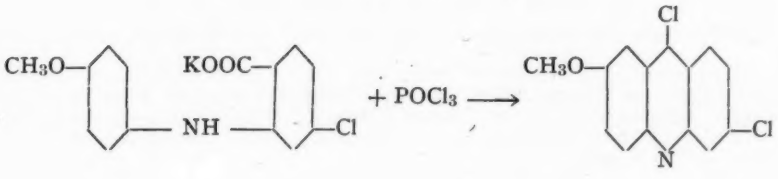
A solution of 40 kg. of potassium hydroxide in 40 liters of water is run in slowly with the aid of a glass separatory funnel. The alkali solution should be added carefully to reduce foaming and the time usually required to run in the 40 liters varies from 1 to 1½ hrs.

The reactor is then closed and the contents heated slowly to 103-105°C., and this temperature is maintained for 3 hrs. Following the heating period, 300 liters of cold water, 3.0 kg. of "carbo-paraffin" (decolorizing charcoal), and 0.7 kg. of potassium sulfide are introduced into the reactor. The temperature is again raised to 103-105°C. and is held there for ½ hr., after which the reaction mixture is filtered through a previously warmed filter press, 3 kg. of filter aid having been added. The clear filtrate is run to another 500-liter reactor, and the original reactor and the filter press are washed with 50 liters of hot water in preparation for the next batch.

The intermediate crystallizes from the filtrate after it has cooled to 15°C. with stirring overnight, and the crystals are separated on a Buchner funnel. The crystals on the filter are washed with two 20-liter portions of water and the wash water is added to the dark blue mother liquor for subsequent evaporation and crystallization. The product, consisting of light gray crystals, is dried for four days at 80-90°C.

The yield averages 70 kg., which is equivalent to 78.5 per cent of theory, based on 2,4-dichlorobenzoic acid.

2. Preparation of 2-Methoxy-6,9-Dichloroacridine Phosphoric Salt (Halocrine Phosphoric Salt)

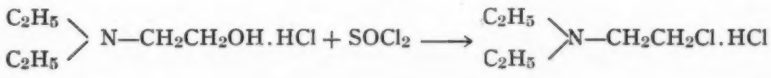


A 300-liter reactor is used for this step. The reactor is also fitted with a stirrer, a steam jacket, and a reflux condenser. Connection to a surface condenser is provided.

Monochlorobenzene (180 liters) and 33 kg. of the "potassium dicarbon" made in the first step are placed in the reactor. After heating to 130°C., 20 liters of the solvent are distilled off to remove all traces of water, and the reactor is then connected to the reflux condenser. Now 25 kg. of phosphorus oxychloride are run into the reactor at such a rate that 2 hrs. are required for the addition of the entire quantity. The reaction mixture is kept boiling during the addition of the phosphorus oxychloride, and for 2 hrs. more.

The reactor is then connected to the surface condenser and an additional 30 liters of monochlorobenzene are removed by distillation. The mixture remaining in the reactor is cooled to 30°C. with stirring, and is transferred to a 500-liter reactor for use in the eighth step of the synthesis.

3. Preparation of 2-Chlorotriethylamine Hydrochloride (Novolid Salt)



2-Diethylaminoethanol hydrochloride ("Novolsalz") was obtained from the I. G. plant at Hoechst. Seventy kg. of this material are introduced into a 300-liter enamel-lined reactor equipped with a stirrer. The reactor is heated in a water bath. Two equal portions (30 kg. each) of thionyl chloride are added, the first portion being run in rapidly at room temperature. Hydrogen chloride gas and sulfur dioxide are evolved and the temperature climbs to 35-40°C. The thionyl chloride addition causes the material in the reactor to become liquid and the mixture is stirred for ½ hr. after all the first portion is in. During this period the temperature in the water bath is raised to 55-60°C., bringing the reactor contents up to 50°C. The second portion of the thionyl chloride is added slowly over a period of 1 to 1½ hrs. This addition raises the reactor temperature to 55-57°C., and causes a copious evolution of hydrogen chloride and

sulfur dioxide, which are removed from the reactor vent gases by means of a scrubber.

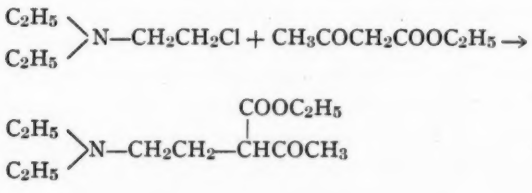
The mixture is allowed to stand for several hours and the temperature is then brought to 70-75°C. On cooling, the mixture solidifies to a crystalline mass and this is removed and dried. The yield of novolid salt is 11 kg. or 99 per cent of theory.

4. Preparation of 2-Chlorotriethylamine (Novolid)

This step consists of obtaining the novolid base from the novolid salt. It is accomplished by dissolving 33 kg. of the salt in 33 liters of water, followed by the addition of 10 kg. of ice. Now a solution composed of 33 kg. of solid potassium hydroxide, 5.4 kg. of a 30 per cent solution of sodium hydroxide, and 22 liters of water is added to the above mixture with stirring.

The mixture is then extracted for ½ hr., using 16 kg. of benzene, followed by a second extraction with 10 kg. of this solvent. Water is removed from the combined extracts by treatment with calcium chloride for approximately 20 hrs., using about 1 kg. of the drying agent. The solution is filtered for use in the next step.

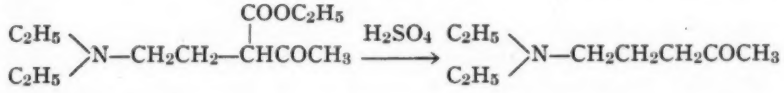
5. Preparation of Ethyl α-(2-Diethylaminoethyl)-Acetoacetate (Novolester)



Into an iron reactor, provided with a stirrer and a reflux condenser, are placed 360 kg. of benzene, 150 kg. of ethyl acetoacetate, and 22 kg. of metallic sodium cut into small pieces. After cooling this solution to 50°C., the benzene solution of novolid from the previous step is added slowly, the latter solution being warmed to 50-60°C. before the addition. Four batches from Step 4 are needed for each batch in Step 5.

After refluxing for 3 hrs., the mixture is cooled and the separated sodium chloride is removed by filtration.

6. Preparation of 5-Diethylamino-2-Pentanone (Novolketone)



Four enamel-lined reactors are used in this step. Each has a capacity of 300 liters and is fitted with a reflux condenser and a steam jacket.

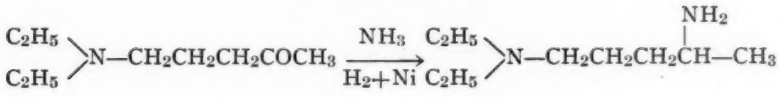
The benzene solution of novolester from the previous step is divided into four equal portions which are distributed into the four reactors. Seventy-five kg. of ice, 25 kg. of water, and 35 kg. of 96 per cent sulfuric acid are added to the solution in each reactor. Steam is introduced into the jacket and the benzene is distilled off. The boiling mixture is then refluxed for 12 hrs.

The mixture is cooled to 30°C. and is transferred to a 300-liter iron reactor provided with a stirrer. The novolketone is separated by the addition of 188 kg. of a 30 per cent aqueous solution of sodium hydroxide and 50 kg. of ice. After removal of the crude ketone, the alkaline solution is extracted with 35 kg. of benzene, and the extract is combined with the crude product. The solution is filtered and dried, followed by removal of the benzene.

The crude ketone is distilled into three fractions. The first fraction comes over at 60-90°C. and 30 mm. pressure, and amounts to 2 or 3 kg. This is called the novol fraction. The second fraction distills at 80-88°C. and 19 mm. pressure, and weighs from 3 to 4 kg. It is called the middle fraction. Pure novolketone comprises the third fraction which comes over at 74-76°C. and 4 mm. pressure, and amounts to 85-85.4 kg. (71 per cent of theory). The novol and middle fractions are combined and redistilled.

The ketone was prepared in this manner until the end of 1942, after which time novolid was condensed with dry solid sodium acetoacetate. About 80 kg. of pure ketone are obtained from 123 kg. of sodium acetoacetate, 290 kg. of dry benzene and about 200 kg. of novolid-benzene solution. The latter is produced from 132 kg. of novolid salt and 104 kg. of benzene.

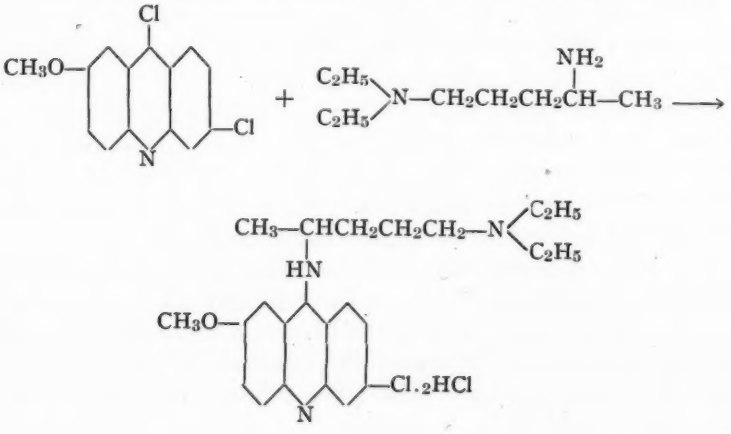
7. Preparation of N′, N′-Diethyl-1, 4-Pentanediamine (Novoldiamine)



A 250-liter iron hydrogenation vessel is used for this step. Into this are placed 50 kg. of novolketone, 100 liters of methanol, and 2 to 5 kg. of nickel contact catalyst. Hydrogen is employed to displace the air in the equipment, and this in turn is displaced with 16.7 kg. of ammonia gas and 1.5 kg. of hydrogen, giving a pressure in the vessel of 30 atmospheres. The pressure is raised to 50 atmospheres by heating the vessel to 95-96°C. Additional hydrogen is led in to maintain the pressure at 50 atmospheres until no further hydrogen is taken up. Between 6 and 6½ hrs. are required for hydrogenation. During the first 10 min. of the process the hydrogen is absorbed rapidly, but after that the reaction proceeds slowly.

The reaction mixture is then cooled, filtered, and distilled, yielding between 45 and 46 kg. of novoldiamine (90-92 per cent of theory). The product boils at 70-71°C./5 mm. From ½ to 1 kg. of residue results in this process.

8. Preparation of Atebrin [6-Chloro-9-(4-Diethylamino-1-Methyl-Butylamino)-2-Methoxy-Acridine Dihydrochloride]



The halocrine phosphoric salt from Step 2 is used as prepared in that step, i. e., in monochlorobenzene solution. Eighty kg. of phenol (at 80°C.) and 26 kg. of pyridine are mixed together in a 500-liter reactor and the batch is allowed to cool to 70°C. The entire lot of solution from Step 2 is then run in and the contents of the reactor are warmed to 40-50°C. The batch is stirred for ½ hr. and the temperature is brought slowly up to 110-120°C. and maintained there for an hour. Then 17 kg. of novoldiamine are added in increments during ½ hr., followed by stirring for ¾ hr. at 110-120°C. The benzene is distilled off at reduced pressure (50 mm.) and the temperature of the reactor contents is again raised to 120°C.

After the batch is cooled to 90°C., it is run into a 1000-liter enamel-lined vessel containing 150 liters of 30 per cent aqueous sodium hydroxide. Four hours stirring at room temperature is said to be adequate but overnight stirring is preferred to guarantee a satisfactory product. The resulting base is filtered off, washed with water, converted to the hydrochloride, and crystallized from acetone.

The yield is 40 kg. or 75 per cent of theory, calculated on the amount of "potassium dicarbon" used.

For comparison with American practice in this final step, the paper by Jones, Shaw and Waldo (3) should be consulted. They describe the condensation of 2-methoxy-6, 9-dichloroacridine with N′, N′,-diethyl-1,4-pentanediamine (also called 1-diethylamino-4-amino-pentane) by heating the two intermediates together in the presence of a much smaller quantity of phenol than that recommended by previous investigators. Other improvements in the last step of the process are also recommended in this paper.

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STANDARDS OF TOLERANCE FOR PROFESSIONAL PHARMACY

By Samuel W. Goldstein, Ph. D.* †

PRACTITIONERS of pharmacy can be divided into two major classifications: Manufacturing Pharmacists and Compounding Pharmacists. The manufacturing group are concerned with the marketing or detailing and the distribution of their products in addition to their pharmaceutical activities. A large proportion of the compounding pharmacists are concerned with the merchandising of the manufacturers' products and with many non-pharmaceutical services in addition to their prescription-counter activities. A growing group of pharmacists are limiting their extra-pharmaceutical services and many of them have united to form The American College of Apothecaries, a subsidiary organization of the American Pharmaceutical Association. Many merchandising pharmacists are growing prescription-department conscious and are developing fine prescription-counter service. Practically all of the pharmaceutical manufacturers maintain control laboratories and the larger manufacturers have developed scientific research laboratories and have assembled scientists whose contribution to the public health is beyond our powers of estimation. Certainly the reputable manufacturing pharmacists taken as units represent the best in one phase of professional pharmacy. Nevertheless it is customary to think of the individual compounder at the prescription-counter as the professional pharmacist. We often, though not often enough, hear a pharmacist praised for conducting "a really professional pharmacy."

How precisely or professionally do the two groups function in their pharmaceutical activities? If the answer is to be based upon actual comparison of the concentration of ingredients in similar official preparations, it is obvious that the prescription-counter compounder will suffer. The difference in precision represents the extent to which the factors influencing precision in compounding can be controlled under the two methods of operation. These factors, and the manner and extent to which they influence compounding precision, have been discussed at length in a series of articles in the

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† The conclusions presented in this article represent the personal opinion of the author.

Practical Edition of the *American Pharmaceutical Association Journal* (1) (2) (3) (4). We can determine how accurately the manufacturer is meeting the standards set in the United States Pharmacopoeia and National Formulary for official products and how closely he adheres to labeled concentrations on his unofficial products. It is obviously unfair to evaluate the accuracy of prescription-counter products on the basis of the same standards of tolerance. Why are manufacturers' products so much more accurate as a rule than the retail compounders' products; and has it always been so? It has not always been so. The major portion of all the restrictive drug legislation was formulated and enacted to reduce the erratic and fraudulent activities of some of the manufacturers in the not too distant past. The effective labeling provisions in the Federal and State laws removed to a great extent the fraudulent nostrums. Establishment of the U. S. P. and N. F. as books of standards for manufactured pharmaceuticals was mainly responsible for the development of control laboratories with the resulting splendid record of precision in the consequent products. To my knowledge, no Federal law exists which is designed to set specific standards for prescription-counter products. Some laws do include the statement that the products used in making medicinals should meet the official standards. The pharmacy law of the State of New Jersey grants authority to the Board of Pharmacy to establish reasonable tolerances for prescription ingredients. This law, passed in 1933, represented the first attempt to establish legal prescription tolerances.

How does this situation affect the overall precision of prescription-counter compounding? The individual pharmacist is practically left to set his own limits of precision. The majority of the pharmacists, I believe, are sufficiently impressed with their professional value and duty to the community to set sufficiently rigid standards for their pharmaceutical activities. Certainly, graduates of recognized Colleges of Pharmacy who abide by the Pharmaceutical Code of Ethics are professional pharmacists, and their products should meet any reasonable standards for prescription-counter compounding. I have found that the great majority of pharmacists in Maryland can meet the U. S. P. and N. F. standards for extemporaneously prepared official products most of the time. A more difficult problem is encountered when unofficial products are tested. Surveys in four states have shown that extremely wide deviations are detected in

preparations purchased from pharmacists, and that this is especially so when the pharmacists do not know that the purchases are being made for testing purposes (5). Establishment of official standards for manufactured products has resulted in a tremendous improvement in manufacturing precision. I believe that establishment of reasonable and equitable standards of tolerance for extemporaneously compounded pharmaceuticals would have a comparable effect. These standards must take into consideration the factors beyond the control of the retail pharmacist. They should be representative of products compounded by practicing pharmacists at the prescription-counters of properly supervised pharmacies. A system for the determination of such standards has been reported in the aforementioned series of articles. The proposed standards have met with approval from many individuals representing the various fields of pharmacy. They also have met with disapproval. At one meeting they were denounced by a manufacturing pharmacist as being too lenient when compared to the standards he must meet. At the same meeting they were denounced by a retail pharmacist and a hospital pharmacist as being too severe. These two pharmacists further illustrated the attitude of many pharmacists by appealing to a physician for his opinion. Too many pharmacists believe that as long as the physician is satisfied that the pharmacists' medicines do not kill his patients, they are performing their compounding satisfactorily. It is this small group especially whose precision could be improved by having reasonable standards to guide them. These reasonable standards should be rigid enough to limit the effect of the medicinal to the desired therapeutic range and thus protect the patient. These standards should not be so stringent that procedures necessary to insure adherence to them would raise the cost of medical care. I believe that the standards of tolerance evolved by the proposed system meet these requirements. These tolerances are obtained by determining the average percentage deviations with which a large number of practicing pharmacists, having different degrees of natural skill, can prepare typical pharmaceutical products under approved conditions. These averages are of course much lower than many of the individual results. I have assumed that, under the special conditions of purchase, these average deviations represent errors caused by factors beyond the control of most of the pharmacists. Assuming that four times the average error accounts for all the

controllable and uncontrollable factors influencing accuracy, then half this product should account for the uncontrollable factors. Therefore twice the average percentage deviations indicate the permissible tolerances. The tested samples are purchased by a known drug inspector of the State Drug Authority to eliminate as much as possible the factor of carelessness in their compounding. The standards thus should represent the best work of the pharmacists rather than their usual compounding precision.

There is another reason why nationally recognized standards for prescription-counter products should be established. Periodically Food and Drug Officials in the course of their necessary and important activities pause to examine the analytical records they have accumulated. The only pharmaceutical standards these Officials have upon which to base their conclusions and decisions with respect to U. S. P. and N. F. drug samples are those given in the official compendia. For unofficial drugs, some of these Officials allow what appears to them to be a very liberal tolerance of $\pm 10\%$. Officials in different states have unlike opinions with regard to these standards and some of them interpret these tolerances more liberally than others. This results in the existence of a confused condition under which the same extemporaneously compounded products may be condemned as illegal in some states while they are considered to be acceptable in other states. Those Officials who place a strict interpretation upon the present standards in their application to prescription-counter products are amazed by the seemingly poor work that is dispensed by a group that is jealous and proud of its professional standing in the community. Some of them cannot refrain from exposing what they consider to be an undesirable condition. Such expositions have been made in the public press with resultant loss of prestige by the whole pharmaceutical group. It is only fair to note that the Officials who have taken this step have usually exhausted all their resourcefulness in attempting to "correct" the situation by other means including legal prosecutions. Until officially recognized reasonable standards for prescription-counter products are made available to all Food and Drug Officials, the pharmacists, good and bad, will suffer from attacks upon their professional ability and integrity.

Establishment of reasonable standards is not offered as a panacea for inaccurate compounding. I believe that an intensive and

continued campaign against carelessness at the presecription-counter is absolutely necessary to make some pharmacists conscious of their carelessness. Hardly any of the wide deviations noted in prescription-counter products are intentional. They are usually due to carelessness or to attention that is divided between the prescription-counter and other store activities. One pharmacist explained the 1% concentration of two 3% preparations requested of him in 3-ounce quantities as follows. He calculated the amount required to make 1 ounce of a 3% solution. He was called to the front of the store and carried the number of grains in his head. When he returned to the prescription-counter he weighed that number of grains of each of the two ingredients for the different solutions. On the same day another pharmacist, in a store two miles from where the above samples were purchased, dispensed these same two 3% solutions. Analysis proved they each contained 1% of the requested boric acid and potassium permanganate respectively. On the next day a pharmacist dispensed a 1% solution of boric acid to a known inspector who had requested 3 ounces of a 3% solution. This pharmacist later realized his mistake and prepared another solution which he asked to have substituted for his first sample. The second sample was found to be a 2% solution. These cases are cited to verify a contention offered by several observers that wide deviations are encountered more frequently in those preparations which require some mathematical step, no matter how simple, in their preparation. Reasonable standards will not make products such as these seem any better. It is such preparations that drive Food and Drug Officials to extreme measures. But reasonable standards will enable these Officials to obtain a fairer overall picture of the accuracy with which extemporaneous compounding is practiced. When based upon reasonable standards, 85% to 90% of the samples purchased by known inspectors will fall within the permissible tolerances. The other 10% to 15% of the samples will show deviations varying from just outside the standards to very wide deviations as shown above. The percentage of samples showing extremely wide deviations is very small. These figures show how accurately prescription-counter products can be compounded. We still are faced with the problem of bringing the pharmacists' products that are prepared for the public, as reflected in samples purchased by inspectors unknown to the compounders, within these limits.

Although prescription-counter precision has been unfairly attacked at different times, the fact remains that there is much room for improvement in this field of pharmaceutical activity. Establishment of reasonable and equitable standards of tolerance for prescription-counter products should rationalize extreme criticism by non-pharmacists. Such standards, I believe, will be helpful in improving compounding precision and consequently in increasing the prestige of professional pharmacy.

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MAKING BIG ONES OUT OF LITTLE ONES

By T. Swann Harding

THAT'S what man does when he makes synthetic fibers. He tries to get molecules to polymerize, to make big molecules out of little ones. He strives also to get nonfibrous molecules which occur in nature into the right shape to form fibers. Perhaps you were unaware that molecules, like bathing beauties, have shapes, but that is a fact.

The molecules in your hair are curled up like springs. Your hair is a protein containing sulfur. Hence it is made up of long chains of amino acids, compounds much simpler than proteins and to the number of two dozen, which nature can combine in huge molecules and in a wide variety of ways. The molecules of your hair can be straightened out, if the hair is stretched and heat and moisture are applied; that produces a permanent wave, but it also uncurls the molecules.

The molecules of hair like those of wool are held together by what chemists call side linkages, the links usually being the amino acid cystine, which contains sulfur. Steam breaks these linkages, which explains why wool can be steam-pressed to a shape it will hold indefinitely. But hot water makes the springlike molecules contract still further, hence it causes shrinkage in wool.

Technicians can use materials intelligently only by understanding their molecular structure. Work on the structure of big molecules influences the bread-making, paper-making, stocking, rubber, plastic, and many other industries. The molecules must be handled properly if synthetic fiber is to be produced.

Many of us remember when rayon was about the only synthetic fiber of any consequence and even it had an iniquitous reputation. But things are very different today and rayon itself has been so improved as adequately to find a multitude of uses. Yet, until 1935, this synthetic fiber made from cellulose was the only one in commercial production in the United States. Actual production began about 1911, after one or two abortive attempts.

Production and the quality of rayon have both steadily improved. Today rayon ranks second to cotton and is consumed at

a rate of 875 million pounds annually. But the production of synthetic fibers other than those made from cellulose—which forms the chief part of ordinary wood and paper—was in its infancy before World War II. Glass fiber is the oldest of the noncellulosic man-made fibers, since its production began in 1936, but the early output was limited.

Two years later production of Vinyon—a fiber made from Vinylite synthetic resin—began, but the output is still small. Commercial production of Nylon yarns began in December 1939, following a short period of pilot-plant production, though this seems almost impossible to believe now, in view of the fiber's tremendous wartime production and its present common use. But the whole synthetic-fiber industry is of recent origin.

As investigation proceeded it was natural that the production of synthetic protein fibers should assume importance. For silk, wool, and mohair are proteins. They are compounded something like a piece of steak. At least they are composed of chains of the same score or more amino acids which combine in various ways to form all proteins.

The properties of these fibers depend on the kinds of amino acids composing them, on the sequence in which the acids are arranged along the chains comprising them, and on the shape of the protein molecules. A big part of the problem consists in finding methods to straighten out globular or curled-up molecules.

Finally, the length of the chains, their form in space, and whether the molecules tend to run along in line or, instead, to cross the line, all count heavily. Scientists engaged in research on these problems have to consider the size and shape of the molecules composing different natural and artificial fibers, as well as those which compose the protein substance that is to be transformed into fiber. They must use the X-ray and other refined equipment to determine the molecular structure of fibers and to find out just what it is that imparts to them their specific properties.

Especially interesting in the last decade has been the development of protein fibers from milk casein and from the proteins in soybeans, corn, egg white, feathers, fish albumin, and peanuts. These fibers often approximate in quality and potential use the natural fibers of wool, mohair, and silk. Indeed the name Azlon has recently been suggested officially as a generic term for synthetic pro-

tein fibers, just as rayon has now come to designate all such fibers with a cellulose base.

Commercial production of a casein-base fiber—wool from milk—began in this country in 1941. About the same time pilot-plant production of a protein fiber derived from soybean protein also got under way, and semicommercial production of a fiber made from peanut protein is now being carried on in England. These synthetic protein fibers are right now at just about the stage of development rayon occupied some thirty years ago.

So far they are comparatively weak, especially when wet, and are generally used in textiles only when blended with natural fibers. However, when so utilized they often impart warmth and other new properties. But technically the protein-fiber industry is in a position to make rapid progress, because there now exists a mass of accumulated knowledge regarding synthetic fiber technology. Now suppose we return to the two most esteemed natural fibers, silk and wool, and see what makes them tick.

Silk differs from all other proteins in its high content of two very simple amino acids, glycine and alanine. Because it contains amino acids in such small variety and does not specialize in those essential to the human body it would make a very poor substitute for roast beef. In fact the two acids named comprise three-quarters of silk, serine and tyrosine making up most of the remainder.

These are all relatively simple amino acids with small molecules. Hence, when polymerized—which means making big molecules out of little ones—they pack together well with their neighbors and this gives silk its smooth surface. Moreover, because the molecules line up well along the fiber and do not tend to traverse it, silk has good tensile strength. Silk therefore is composed of thin, linear, well-extended chains of molecules all in stable form.

Wool offers an interesting comparison. Its molecules are of the pudgy or bunchy sort. For wool is composed of a considerable number of quite complex amino acids with big molecules. One of them, cystine, contains sulfur. It forms bridges and binds the molecules of wool into giant molecular aggregates, hence wool has a rough surface. As compared with silk, wool's tensile strength is low; like silk it loses little strength when wet with water though, unlike silk, it can be stretched far when wet but will assume its original shape on release.

Wool makes crease- and crush-resistant fabrics because its molecules easily snap back into place after the fiber is stretched. You might almost say that their chains of amino acids fold and unfold, though the elasticity of wool differs from that of rubber, in which the chains kink and curl in random fashion. Wool fibers are not stable when stretched because wool molecules, bound together by sulfur-containing cystine, are bunchy and fold over one another. But steaming breaks these cystine bridges and wool then gets a permanent set.

Now suppose we take a look at a protein which we carry around in our own bodies. It composes much of our connective tissues and the organic substance in our bones. It is called collagen. It differs very materially from wool and silk, as do most natural proteins from which science and technology try to make synthetic fibers. For one thing it has a high content of two amino acids called proline and hydroxyproline and the former in particular has a very peculiar shape. It strings along fibrously in the middle but has bunches at both ends.

That makes it simply impossible for collagen to form extended chains like those in silk or in stretched wool. Neither does collagen exhibit the long-range elasticity that wool has. The scientist's job here is to straighten out collagen's kinked chains, or else force them to slip over one another and thus stretch collagen into a fiber, and that is very difficult.

Then again collagen absorbs about six times as much water as wool and nine times as much as silk, and it then swells much more than either. That is in part because it contains less of the sulfured amino acid cystine than does wool. To overcome its water-absorbing tendency collagen must be treated chemically in a process that somewhat resembles tanning a hide to make leather. To make things harder, collagen is so complex that no model of it has yet been made, though accurate models exist to show just how silk and wool molecules fit together.

The proteins of milk, corn, eggs, soybeans, feathers, and peanuts are all complex. They all—except feather protein—tend to have globular shapes. To make artificial fibers out of them the scientist has somehow to untangle those globules and extend them into linear chains. Yet this he has done in many instances, using

the X-ray and other devices to trace the conversion from globular to fibrous state.

From the standpoint of composition, bulkiness, and the nature of the chains of molecules, along with other observed properties, fibers made from milk, egg, or soybean proteins should pack their molecules rather as does wool. Actually fabric made from milk casein does resemble wool in feel and in some other qualities. But the strength of these fibers has to be built up considerably yet to make them equal that of natural protein fibers. Manufacture of the casein fiber, Aralac, was begun on a pilot-plant basis in this country in 1939, commercial production getting started two years later.

The scientist's problem in producing an artificial fiber with a specific set of desirable characteristics is to assemble and arrange the molecules so that the desired qualities will appear. This is a very high type of tailoring indeed, far removed from that performed on fabric in making a suit. Of basic importance is knowledge of how the chains of molecules are arranged around the axis of the fiber.

Primary bonds within molecules which hold them together are much stronger than secondary bonds, like the cystine bridges, which hold molecules to molecules, as in wool. Rupture of a fiber occurs because its chains of molecules slip apart. But if the chains all run in the direction of the fiber's axis it is very difficult to separate them and break the fiber. However if the chains traverse the axis they break readily because they easily become unzippered.

So far it has proved impossible to confer very great strength on wet synthetic protein fibers. Hence various hardening treatments with chemicals like formaldehyde are used to stabilize them by forming cross links between the chains. But in time the requisite protein molecules will be straightened out and formed into the kind of linear chains desired. It is a matter of somehow unfolding and rearranging along fiber axes the globular molecules which had previously been folded into compact, near-spherical particles by old Dame Nature.

For a specific instance take the lowly goober or peanut. The first obstacle in developing a protein fiber from the peanut is the red coloring matter of the skin which, if not removed, carries through to the finished product. If the skin is removed by blanching, that is not only costly, but the process so damages the protein that it cannot be used in fiber making. So a method of removing the skins

by lye treatment was developed which did not injure the protein and cost less than a tenth of a cent per pound of peanuts.

Next an oil-free meal must be made from which a satisfactory protein can be extracted. Meals produced by hydraulic or screw-press processes will not do both because they still contain some oil and because the temperature of processing injures the protein. So a solvent-extraction process, developed by the Department of Agriculture's Southern Regional Research Laboratory for soybeans, and now being applied also to cottonseeed, was tried and proved satisfactory.

A hundred pounds of peanut meal will yield about 33 pounds of protein fit for use in fiber, a residue which has an animal feed value equal to 33 pounds of the original meal, and 16 pounds of minor components in solution, many of which will prove industrially useful, especially for growing yeast for feed and food purposes.

The equipment used to produce fiber from peanut protein is quite similar to that used for rayon. Except that different chemicals are used to prepare the spinning solutions and to stabilize the spun fibers, the processing is also similar. Research now centers on improvement in fiber quality, in short on the old problem of uncoiling those globular molecules, arranging them in line along the fiber axis and stabilizing them in that position.

In this way the structure of a natural protein fiber is approximated. But much more research will be required to perfect this process. However, Sarelon, the peanut-protein fiber so far produced, has about the same wet and dry strength as fibers made from casein or from soybean protein.

Even in their present condition the synthetic protein fibers make excellent fabric blends. They impart to the fabrics properties often unobtainable with other fibers or else, as in the case of wool, obtainable only at a higher price. Thus considerable quantities of milk-casein fiber have been used along with fur to manufacture felt hats of unusual quality. Furthermore, suitable and adequate sources of proteins from which to make synthetic fibers already offers a problem.

Before 1940 the total consumption of all noncellulosic synthetic fibers—or synthetic fibers other than rayon—was inconsequential. But consumption climbed rapidly from 4.5 million pounds in 1940 to 53.3 million pounds in 1946. The latter quantity is small as com-

pared with the cotton, rayon, and wool consumed, but it is already greatly in excess of silk or flax consumption. Where will the protein come from?

Today industrial protein is available only in by-products, the value of which is less than that of the principal products, hence the quantity is limited by the demand for the primary products, and industrial users compete directly with consumers of the by-products. The production of soybean oil limits the amount of soybean presscake protein available, and so on.

At present the main source of protein used in industrial fiber manufacture is casein obtained almost wholly from the skimmed milk produced in commercial creameries, plus some imports. In prewar years this totaled 30,000 tons annually, but only part of it was obtained by processes that rendered it fit for fiber production. During recent years about 5,000 tons of it have been so used annually.

But suppose large-scale expansion of the synthetic-protein fiber industry was contemplated. That would be impossible if the fiber must all be made from casein. Even moderate expansion would create severe competition with established users of casein for other purposes, so new sources of industrial protein are already urgent.

The three largest potential sources are the seeds of soybeans, cotton, and flax, for proteins from the packing-house and fishing industries are already in full commercial use. Oil is the primary product of these seeds; it determines prices paid to growers. The presscake, containing about 35-40 per cent of protein, is a byproduct amounting to over six million tons annually, but an expanded protein fiber industry would want more than this.

How about peanuts? During the war we produced about a hundred thousand tons of peanut presscake a year as a by-product of crushing peanuts for oil for war use. But before the second world war peanuts were essentially peanuts, small-time stuff eaten roasted, salted, in butter, or confection. Yet they could be grown and crushed in large quantity if demand for the oil were sustained, though at present they offer no greater source of protein for industrial use than does casein.

The above-mentioned Southern Regional Research Laboratory has developed a successful process to produce from peanuts a protein that can be processed into synthetic fiber. Furthermore the owners of many new solvent-extraction plants now intend to proc-

ess peanuts as well as cottonseed, thus soon rendering limited quantities of peanut meal available for industrial use. Undoubtedly it will be snapped up, but it would take tremendous expansion of this sort of thing to develop a large-scale synthetic protein-fiber industry.

Work by Robert B. Woodward of Harvard, co-synthesizer of quinine, points to another solution of the problem. For he has succeeded in producing artificially what he calls protein analogues and what are essentially real, honest-to-goodness proteins. This has never been done before. Whereas earlier German investigators many years ago succeeded in tying together only eighteen or twenty amino acids to form polypeptides, things with much smaller molecules than proteins, Woodward has now made chains of ten thousand links.

To all intents and purposes he has made proteins on a laboratory scale and that almost puts him in a class with Dame Nature herself. He has mastered the complex process of polymerization in this field, making big ones out of little ones—molecules, not stones, that is. His work will ultimately affect not only the chemistry of antibiotics and of the viruses but the synthetic fiber industry.

In the future, therefore, the technologist may not start off by trying to uncoil a globular protein Nature fixed into that form with designs of her own, and which it is the devil's own job to get to string out along a line and make into a strong fiber. He may instead add together the particular varieties of amino acids arranged in the particular patterns and sequences to produce a protein fiber with precisely the strength and other properties desired for a particular purpose.

So a race is on between two feasible methods of producing synthetic protein fibers. Bets may be placed with assurance as we may be absolutely certain that our chemists and technologists will solve this problem by one means or another just as they did that of perfecting an atomic bomb and a powerful and reliable wartime insecticide.

SELECTED ABSTRACTS

Barrier Creams. S. G. Horner. *Pharm. J. 106, 7* (1948). Barrier creams, which are intended to protect the skin of industrial workers against the irritation of chemicals or the accumulation of dirt in the pores, are of two types: *(a)* those used against undiluted oils and solvents, and *(b)* those used against aqueous solutions of chemicals. Each type must meet four requirements:

1. In order to be non-irritant, the pH of the preparation should approximate that of the skin, viz., 5.5-6.5.

2. It must be insoluble in the substance against which it is intended to give protection.

3. After application, the cream should not leave the hands slippery or sticky since this would involve danger in the use of tools.

4. The cream must be easily removable by ordinary cleansing methods not requiring the use of special removers.

Oil-proof barriers. A vanishing cream may be used; a suggested formula consists of stearic acid 20, sodium carbonate 2, glycerine 6, and water 78.

Water-soluble ointments, emulsions or solutions have the disadvantage of being easily removed by sweat. To correct this fault, they are sometimes mixed with fats and oils. Ingredients such as methyl cellulose, sodium alginate, tragacanth, acacia and casein are used in the water-soluble preparations. One formula of this type includes acacia 5, tragacanth 5, borax 2, and water 88.

Waterproof barriers. These fill the follicles of the skin with a harmless fat which repels water-soluble irritants. A light-deflectant is sometimes added, since it has been observed that light may alter the composition of certain substances, thereby rendering them more irritant. Tetryl, e. g., is converted by the action of light to methyl picramide, a compound very irritating to the skin. The addition of a synthetic wetting agent may facilitate removal of the cream. A simple preparation suggested contains soft paraffin 3 parts and lanolin 1 part.

Modern emulsifying agents may be used to produce O/W or W/O emulsions according to the choice. An example of such a preparation contains Lanette wax SX 10, peanut oil 20, soft paraffin 20, and water 50.

Toxic absorption barriers. Animal fats should not be included in barrier creams designed to protect against such toxic substances as T. N. T., nitrobenzene, aniline compounds, pitch, and tar which possess carcinogenic properties, since the local or systemic effects may thus be aggravated.

Dihydroergocornine in Hypertension. H. J. Bluntschli and R. H. Goetz. *S. Afric. Med. J.* June 14, 1947; through *Pharm. J. 105,* 434 (1947). Dihydroergocornine (DHO 180) has been prepared by Sandoz, Ltd., but is not as yet available on the open market. It is one of four well-defined crystalline compounds prepared by the hydrogenation of three alkaloids obtained as a mixture from ergotoxine. These hydrogenated derivatives, the others of which are dihydroergotamine, dihydroergocrystine and dihydroergokryptine, are less toxic but more sympathicolytic than the original alkaloids.

In trials of the effect of dihydroergocornine on the blood pressure of 38 normal and hypertensive subjects, it was found that small doses have a more powerful depressor effect in cases of essential hypertension than in the normal. The doses producing toxic effects in hypertensive patients are smaller, however, than those required in normal subjects.

Doses of 0.5 mg. were administered intravenously or preferably by intravenous infusion, and intramuscularly, or 2 mg. orally.

2-*p*-Aminobenzenesulfonamido-4:6-dimethoxypyrimidine Absorption and Excretion in Man. H. G. L. Bevan. With Notes on a Clinical Trial in Pneumonia. R. W. Luxton. *Brit. J. Pharmacol. 2,* 163 (1947). A new sulfonamide, 2-*p*-amino-benzenesulfonamido-4:6-dimethoxypyrimidine, or sulfadimethoxypyrimidine, was administered to a series of 80 patients, most of whom were pneumonia cases. In the majority of patients treated with 5 Gm. of drug followed by 3 Gm. every 24 hours, blood concentrations of 8 mg./100 ml. or more were reached and well maintained. Slightly higher

blood concentrations were obtained by administering 3 Gm. every 12 hours, after an initial dose of 5 Gm. In nearly all patients the free drug was present in appreciable quantities 3 days after the last dose.

The average recovery of the drug from the urine was 32.9 per cent, as compared with the following values reported for other sulfonamides: sulfamezathine, 86.2 per cent; sulfadiazine, 68 per cent; sulfapyridine, 57.3 per cent. The percentage of the drug recovered as the acetylated form was low, whether from the blood or urine. No renal symptoms were directly attributable to the observed presence of crystals of the drug in numerous specimens of urine.

Estimation of serum bilirubin, protein, and phosphatase performed on 9 patients gave no indication of gross liver damage.

The drug was subjected to additional clinical trial in 41 cases of pneumococcal lobar pneumonia. The dosage schedule was varied, the initial dose being 3 to 5 Gm., followed by 2 to 4 doses of 2 to 3 Gm. each at 12 or 24 hour intervals. Sulfadimethoxypyrimidine was well tolerated and showed definite therapeutic value, but is considered to be less effective than other sulfonamides in series of similar cases.

Sodium Ascorbate in the Treatment of Allergic Disturbances. S. L. Ruskin. *Am. J. Digest. Dis. 14,* 302 (1947). Previous studies by the author have indicated that although daily dosages of 1 to 2 Gm. of vitamin C produced considerable relief from allergic symptoms in many patients, improvement was either small or lacking in a group of cases displaying a lowered resistance to infection. Gastric irritation was found to result frequently from the high dosage of free ascorbic acid. This suggested that the use of sodium ascorbate might be preferable.

A review of the literature on the interrelationship of the adrenal cortical hormone to vitamin C and sodium led the author to try sodium ascorbate in the treatment of allergic conditions.

Oral sodium ascorbate ("Sodascorbate") therapy in a dosage of 2 Gm. daily produced results which were superior to those experienced with ascorbic acid, particularly in cases which had proved refractory to large doses of the latter. Several intractable cases of

asthma were greatly benefited, and particularly encouraging results were obtained in the treatment of seasonal hay fever. There was marked freedom from gastric irritation.

Increased diuresis was usually noted. It is suggested that sodium ascorbate may exert a favorable action in urinary lithiasis through both the solvent action of the ascorbate on carbonates and the solubilizing action of the sodium ion.

Eight case reports are presented, and twenty-four references to the literature are cited.

Dicumarol Poisoning. A. J. Draper, Jr. *J. A. M. A. 136,* 171 (1948). The successful treatment of a case of hemorrhagic diathesis due to accidental poisoning by self-administered dicumarol is reported. The exact dosage and duration of self-medication could not be ascertained.

The patient complained of backache and reported that the stools and urine had been grossly bloody for two days prior to hospitalization. The author reports the results of physical examination and the laboratory studies. Purple ecchymoses were scattered over various parts of the body; the red blood cell count was 3,740,000; white blood cells, 15,800; hemoglobin 10.0 Gm. (70 per cent); bleeding time five minutes and thirty seconds; coagulation time (capillary tube method) over ten minutes; the prothrombin level was very low.

"Synkayvite" (a vitamin K preparation) therapy was instituted, the patient receiving 30 mg. intramuscularly in divided doses, then 60 mg. intravenously twice at a six hour interval, and a transfusion of 500 cc. of fresh citrated whole blood. The intravenous administration of "Synkayvite" in a dosage of 60 mg. per day was repeated on the second, fifth and sixth hospital days.

The prothrombin level rose to 55 per cent on the fourth day, 90 per cent on the sixth day, and 98 per cent on the eighth day. On the fifth day the coagulation time decreased to two minutes and six seconds, and the bleeding time to one minute and fifteen seconds. On the seventh day the red cell count was 4,500,000, white cell count 7,250, and the hemoglobin level 12.6 Gm. The patient was asymptomatic on the eighth day and was discharged.

The author reviews the published observations on dicumarol, stating that fatalities directly attributable to hemorrhage induced by dicumarol have not occurred in well-followed cases. The necessity of a constant check on the patient's prothrombin level is emphasized by a published report of a fatal case in which a total of 2,100 mg. of dicumarol was administered without one such check.

Chemotherapy of Leprosy. G. H. Faget and P. T. Erickson. *J. A. M. A. 136,* 451 (1948). The authors report their observations in the treatment of leprosy with the sulfone drugs Promin (the sodium salt of *p,p'*-diaminodiphenylsulfone-N,N'-didextrose sulfonate), Diasone (disodium formaldehyde sulfoxylate diaminodiphenylsulfone), and Promizole (4,2'-diaminophenyl-5'-thiazolylsulfone) and also with streptomycin.

Intravenous administration of Promin is preferable, as it is too toxic when given orally. The dose found to give consistently good results with a minimum of toxic effects was 5 Gm. daily. The initial daily dose was 1 Gm., increased gradually. The authors advise discontinuing treatment for one week after each two-week period of daily injections of Promin, in order to allow the patient's hemopoietic system to restore the blood cells lost through the hemolytic action of the drug. In order to detect early evidence of drug toxicity, urinalysis and red and white blood cell counts and hemoglobin estimations were performed every three weeks. Promin is rapidly eliminated in the urine; only a trace or none remains in the blood 24 hours after injection.

Diasone was found to be less toxic than Promin by oral administration. Therapy is started with one 0.3 Gm. capsule or tablet daily, gradually increased to the optimal dose of 0.3 Gm. three times daily. Rest periods of two weeks are advised after each two months of therapy. Periodic laboratory examinations of blood and urine are necessary. Secondary anemia was occasionally found to develop, in which case iron and liver extract were administered. Blood levels of Diasone were found to decrease to a trace 12 hours after the evening dose, the drug being excreted in the urine.

Promizole was administered orally in an initial dose of 0.5 to 1 Gm. three times daily, gradually increased to an optimal daily dose of 6 to 8 Gm. Although toxic effects were rarely observed, frequent clinical and laboratory examinations are considered necessary. The

rapid disappearance of Promizole from the blood parallels that of Diasone.

No crystalluria nor evidence of renal damage was observed following the administration of these sulfone drugs.

The therapeutic effects of sulfone therapy are described, and the number of cases of leprosy treated and the number and percentage of arrested cases secured with Promin and Diasone therapy in relation to the duration of treatment is presented in tabular form. An "arrested case" is defined by the authors as one having twelve consecutive months of negative bacterioscopy including skin and nasal scrapings and being free from any other signs of disease activity for at least one year. Data on Promizole were not included, since only 20 patients had been treated with this drug for too short a period to permit proper evaluation.

Treatment with Promin or Diasone, or both, has been given to 317 patients for varying periods up to six years. In the Promin-treated group of 178 patients there were 31 (17.4 per cent) arrested cases; for the Diasone-treated group of 121 patients, the figure was 7 (5.8 per cent). In a group of 18 patients who received both drugs there were no arrested cases, although it is believed that one patient will soon meet the necessary requirements.

In a series of 10 cases of lepromatous leprosy treated with streptomycin for a period of eight months, encouraging therapeutic effects were noted in some cases but after an initial favorable response the development of resistance to the antibiotic by *M. leprae* appeared to occur. The drug was administered intramuscularly in divided doses totalling 2 Gm. (2,000,000 units) in 24 hours. In 2 cases the dosage was reduced to one-half this amount because of toxic reactions. The authors conclude that the sulfones yield better results in the treatment of leprosy than streptomycin. Laboratory examinations indicate that the sulfones exert a bacteriostatic action in leprosy; and although they act slowly, until further research produces superior chemotherapeutic agents for this use, they must be considered the optimal treatment for leprosy.

Death Following Accidental Ingestion of DDT. N. J. Smith. *J. A. M. A. 136,* 469 (1948). The author reports a fatal case of poisoning resulting from the accidental ingestion of 120 cc. of a commercial insecticide containing 5 per cent of DDT, 2 per cent of

"Lethane" (384 special), and 7 per cent of xylene in deodorized kerosene.

The constituent "Lethane" is stated to be a liquid insecticide concentrate containing 12.5 per cent by volume of β-butoxy-β′-thiocyanodiethyl ether and 37.5 per cent by volume of β-thiocyanoethyl esters of aliphatic acids containing 10 to 18 carbon atoms, standardized with petroleum distillate.

The patient, a 58-year old male, realized his error immediately and drank a quart of milk, followed by several glasses of beer, within a few minutes. The author suggests that there is a possibility that the alcoholic beverage increased the susceptibility of the tissues to a parenchymatous poison.

Frequent and copious vomiting ensued within an hour, continuing for 36 hours, at which time involuntary spastic contractions of the fingers and wrists were present. The patient was then seen and treated by a physician; but as he was not seen by the author until 3 days later, the nature of the treatment was unknown.

Details of the patient's physical condition and of the laboratory findings at the time of admission to hospital are reported. The erythrocyte count was 3,120,000 and the total leukocyte count 11,600. Vomiting continued, the vomitus being blood-stained. The patient was given 1,000 cc. of 10 per cent glucose in isotonic sodium chloride solution, but he soon became comatose and died 30 hours after admission.

The findings on necropsy are presented in detail. Only 2 deaths resulting from DDT intoxication have been reported previously, although the literature contains a few papers on non-fatal cases and a number on the results of animal experimentation. Pronounced tubular degeneration of the kidneys and severe toxic hepatic degeneration were noted.

Experimental studies were conducted on a small series of rabbits. The administration of the original insecticide mixture or of 5 per cent DDT in kerosene produced lesions closely simulating those observed in the patient. No changes in either the liver or kidneys could be demonstrated in rabbits to which proportionate amounts of either xylene or "Lethane" were administered.

BOOK REVIEWS

The Essential Oils. By Ernest Guenther, Ph. D., Vice President and Technical Director of Fritzsche Brothers, Inc., New York, N. Y. Volume I, xvi + 427 pages, including index. D. Van Nostrand Company, Inc., New York, N. Y., 1948. Price $6.00.

Every chemist who is concerned with the essential oils is certain to welcome the appearance of Volume I of Dr. Guenther's new work on this field. The well-known books by Gildemeister and Hoffmann, Parry, and Finnemore have been for years the standard reference sources in this interesting phase of plant chemistry, but there has been for some time a distinct need for an authoritative and up-to-date treatment of the subject.

Probably no other person is in a better position than Dr. Guenther to undertake this task. For more than twenty years he has traveled to all of the regions of the world where essential oils are produced—Europe, Africa, Asia, Australia, and the Americas—for the purpose of procuring accurate data on the production of these oils. In the course of these travels he secured samples of unquestioned authenticity, produced under his direct supervision. This in itself constitutes a valuable contribution, since it has permitted the establishment of criteria for purity and quality of certain oils of previously doubtful origin. In addition, he has taken excellent moving pictures showing the production of the essential oils at their source; doubtless most of the numerous illustrations with which the book is provided have been so acquired.

Volume I is divided into four main chapters, as follows:

Chapter I, titled The Origin and Development of the Essential Oil Industry, constitutes a 13-page summary written by Dr. George Urdang, Director of the American Institute of the History of Pharmacy, Madison, Wis.

Chapter II, covering 68 pages, on The Chemistry, Origin and Function of Essential Oils in Plant Life, was written by Dr. A. J. Haagen-Smit, Professor of Biochemistry at the California Institute of Technology.

In Chapter III, comprising 141 pages, Dr. Guenther discusses The Production of Essential Oils: Methods of Distillation, *Enfleurage,* Maceration, and Extraction with Volatile Solvents. The inclusion in this chapter of a section on terpeneless and sesquiterpeneless oils is of special interest.

Chapter IV, The Examination and Analysis of Essential Oils, Synthetics, and Isolates, covers 140 pages and was written by Edward E. Langenau, Director of the Analytical Laboratories of Fritzsche Brothers, Inc. The subject matter includes modern, proven analytical procedures, and an excellent bibliography of recent references arranged under the appropriate subject headings is a feature which will be highly appreciated by the analyst.

The book includes an appendix which presents a tabulation of various industries which utilize essential oils, a brief discussion of the storage of these oils, various conversion tables, and tables of the boiling points of more than 200 isolates and synthetics at reduced pressures. The latter, which include only substances of interest in essential oil chemistry, are stated to have been selected from the more inclusive work of von Rechenberg, published by Schimmel and Company in 1923.

The entire book is well documented with references to the original literature. The style is clear and interesting, and the quality of paper, typography, and binding is good. Dr. Guenther and his collaborators are to be congratulated upon a careful, painstaking effort. Only a few minor errors of spelling were noted by this reviewer.

According to the publishers subsequent volumes now in preparation will deal with the individual essential oils and their constituents. Their appearance will be awaited with great interest.

A. A. Dodge

Colloid Science—A Symposium. x + 208 pages, including index. Chemical Publishing Co., Inc., 26 Court St., Brooklyn 2, N. Y. Price: $6.00.

The text of this symposium was taken from a series of lectures given as a course in colloid science at Cambridge University. These are concerned with a variety of subjects, including: Surface Chem-

istry and Colloids; Thermodynamics and Colloidal Systems; Physical Properties of Macromolecules; Emulsions *in vivo;* X-ray Analysis of Colloidal Systems; Membrane Equilibrium; Infra-red Spectra and Colloids; and Vinyl Polymerization.

The lectures are interesting and informative, but treating, as they do, selected, specialized topics, it is not likely that the book will be of general interest. Anyone desiring to obtain up-to-the minute, authoritative information on these topics will, however, find it valuable.

LOUIS A. REBER

Pharmaceutical Preparations, Second Edition. By George E. Crossen, Ph. D. and Karl J. Goldner, Ph. D.—250 pages—Lea & Febiger, Philadelphia, 1948—Price $4.00.

This book is intended as a commentary to be used with the United States Pharmacopoeia and the National Formulary by the student in his courses dealing with the manufacture of official preparations. This, the second edition, is based on the drugs of the U. S. P. XIII and the N. F. VIII.

The text is arranged so that different classes of preparations are discussed with the individual members of each class listed alphabetically according to their English title. The authors have avoided unnecessary duplication of material already found in the U. S. P. and the N. F. giving rather some data on the reason for certain steps in the manufacturing process and then discussing the nature of the finished product from the standpoint of its appearance, properties, uses, stability, etc.

Although similar data might be found in some of the larger compendia, it is believed by this reviewer that the book should be very useful to the pharmacy student in particular and even to the pharmacist. Its brief concise style together with the fact that all preparations of the same type are grouped together make it very useful as a text or reference for the laboratory courses in laboratory pharmacy. There is some evidence of over-simplification in the text but possibly for the average student this may not be a disadvantage.

L. F. TICE

Fungicides and Their Action. By James G. Horsfall. Chronica Botanica Company, Waltham, Mass.—1945.

As would be expected, Dr. Horsfall has produced a definitely-stimulating and thoughtfully-written book about a difficult and not-too-well-known field. Dullness is avoided by the unusual ability of the author to express himself simply, clearly and with great common sense.

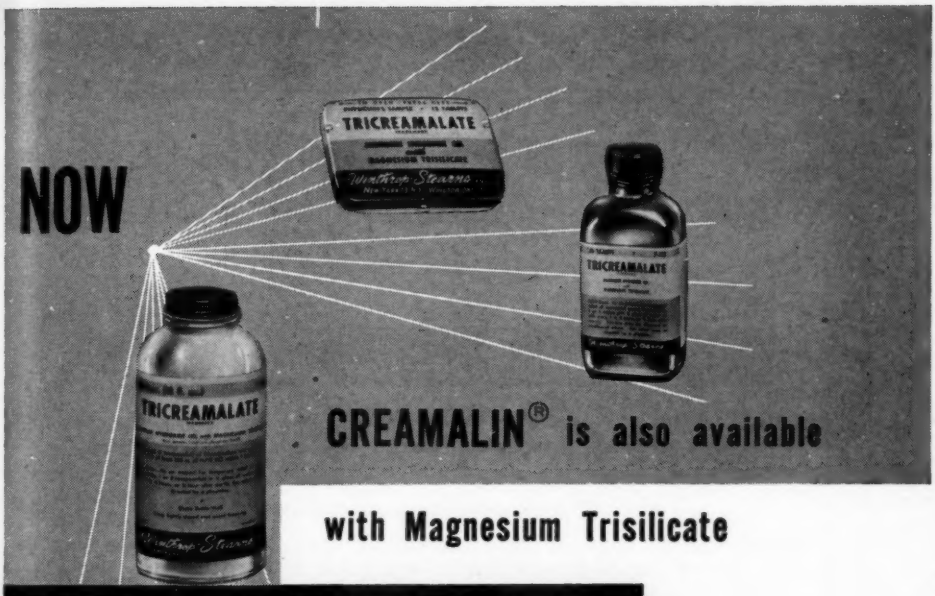
Perhaps the best evidence of what the reviewer thinks of the book is the fact that he has adopted it for use in his own class in advanced mycology, where it has excited critical reading and discussion.

The work deals with the underlying theories of fungicides and their action and does not represent a recipe book crammed with formulae with directions for their use. Emphasis is laid on the intelligent construction and evaluation of the dosage response curve as a tool for the mycologist.

There are particularly good chapters on coverage of single and multiple surfaces, tenacity and the actions of copper, zinc, organic nitrogen and other organic compounds and phytotoxicity. The section on artificial immunization and chemotherapy is of great value, discussing as it does among other things the antidoting of toxins pointing the way for future investigators who may profit by the data being amassed on vascular diseases such as the Dutch elm disease by pioneers in this field.

There is a lengthy and very useful bibliography at the end of the work.

MARIN DUNN



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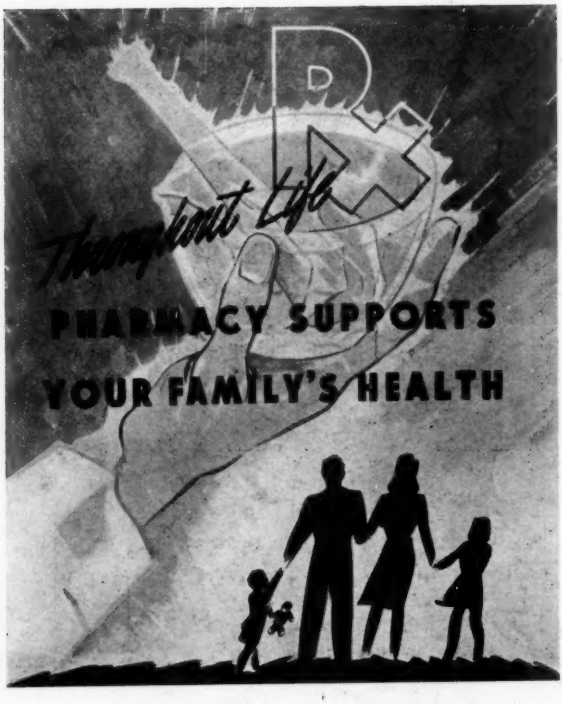
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